Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Management of Medication Toxicity or Intolerance (Last updated March 1, 2016; last reviewed March 1, 2016)

Panel's Recommendations

- In children who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, antiretroviral therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) **(AII*)**.
- When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen **(AI*)**.
- The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity **(AIII)**.
- Dose reduction is not a recommended option for management of ARV toxicity, except for those few ARV drugs (e.g., efavirenz) for which a therapeutic range of plasma concentrations detected by therapeutic drug monitoring correlates with toxicity **(AII*)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents but not studies limited to post-pubertal adolescents

Medication Toxicity or Intolerance

The goals of antiretroviral therapy (ART) include achieving and maintaining viral suppression and improving immune function, with a regimen that is not only effective but also as tolerable and safe as possible. This requires consideration of the toxicity potential of a ART regimen, as well as the individual child's underlying conditions, concomitant medications, and prior history of drug intolerance or viral resistance.

Adverse effects (AEs) have been reported with use of all antiretroviral (ARV) drugs, and are among the most common reasons for switching or discontinuing therapy, and for medication nonadherence. However, rates of treatment-limiting AEs in ARV-naive patients enrolled in randomized trials or large observational cohorts appear to be declining with increased availability of better-tolerated and less toxic ART regimens and are generally less than 10%.[1-11] In general, the overall benefits of ART outweigh its risks, and the risk of some abnormal laboratory findings (e.g., anemia, renal impairment) may be lower with ART than in its absence during HIV infection.

ARV drug-related AEs can vary in severity from mild to severe and life-threatening. Drug-related toxicity can be acute (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For some ARV medications, pharmacogenetic markers associated with risk of early toxicity have been identified, but the only such screen in routine clinical use is HLA B*5701 as a marker for abacavir hypersensitivity.[12-14] For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogenetic marker, CYP2B6 genotype, should be assessed in an attempt to prevent toxicity (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).[13-16] For a few other ARV drugs, known therapeutic ranges for plasma concentrations as determined by therapeutic drug monitoring (TDM) may indicate the need for dose reduction or modification of ART in patients experiencing AEs (see below and Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection).

The most common acute and chronic AEs associated with ARV drugs or drug classes are presented in the Management of Medication Toxicity or Intolerance tables. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies and provide selected references regarding these toxicities in pediatric patients.

Management

Management of medication-related toxicity should take into account its severity, the relative need for viral suppression, and the available ARV options. In general, mild and moderate toxicities do not require discontinuation of therapy or drug substitution. However, even mild AEs may have a negative impact on medication adherence and should be discussed before therapy is initiated, at regular provider visits, and at onset of any AEs. Common, self-limited AEs should be anticipated, and reassurance provided that many AEs will resolve after the first few weeks of ART. For example, when initiating therapy with boosted protease inhibitors (PIs), many patients experience gastrointestinal AEs such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these AEs. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system AEs are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime, on an empty stomach, to help minimize these AEs. They should be advised that these AEs usually diminish in general within 2 to 4 weeks of initiating therapy in most people, but may persist for months in some, and may require a medication change.[17-19] In addition, mild rash can be ameliorated with drugs such as antihistamines. For some moderate toxicities, using a drug in the same class as the one causing toxicity but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required.

In patients who experience unacceptable AEs from ART, every attempt should be made to identify the offending agent and to replace the drug with another effective agent as soon as possible.[20,21] Many experts will stagger a planned interruption of a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, stopping the NNRTI first and the dual nucleoside analogue reverse transcriptase backbone 7 to 14 days later because of the long half-life of NNRTI drugs. For patients who have a severe or life-threatening toxicity (e.g., hypersensitivity reaction—see Hypersensitivity Reaction, Table 12l), however, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the AE has been determined, planning can begin for resumption of therapy with a new ARV regimen that does not contain the offending drug or with the original regimen, if the event is attributable to another cause. All drugs in the ARV regimen should then be started simultaneously, rather than one at a time with observation for AEs.

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible.[22-26] Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is permissible for patients whose viral loads are undetectable. However, substitution of a single active agent for a single drug in a failing multidrug regimen (e.g., a patient with virologic failure) is generally not recommended because of concern for development of resistance (see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy).

TDM may be used in the management of a child with mild or moderate toxicity if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range[27,28] (see Role of Therapeutic Drug Monitoring). This is the only setting in which dose reduction would be considered appropriate management of drug toxicity, and even then, it should be used with caution; an expert in the management of pediatric HIV infection should be consulted.

To summarize, management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate transient side effects.
- If necessary, change from one drug to another drug to which a patient's virus is susceptible (such as changing to abacavir for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor (INSTI) for efavirenz-related central nervous system symptoms).
- Change drug class, if necessary (e.g., from a PI to an INSTI or a NNRTI or vice versa) and if a patient's virus is susceptible to a drug in that class.
- Dose reduction only when drug concentrations are determined to be above the therapeutic range.

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Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	Onset: • 1–6 days after starting LPV/r Presentation *Neonates/Preterm Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) • Non-CNS-associated toxicity may include cardiac toxicity and respiratory complications.	Exact frequency of ethanol and propylene glycol-associated toxicity unknown in neonates receiving LPV/r oral solution.	Prematurity Low birth weight Age <14 days (whether premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	Onset: • 1–2 days after initiating treatment • Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% experienced persistent symptoms at 12 months and in another, half of discontinuations occurred after 12 months. Presentation (May Include One or More of the Following) *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/completed suicide • Seizures (including absence seizures) or decreased seizure threshold	Variable, depending on age, symptom, assessment method Children: • 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation • 9% incidence of new-onset seizures reported in 1 study in children aged <36 months, in two of the children the seizures had alternative causes. Adults: • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related severe CNS manifestations including suicidality.	Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism (CYP2B6 516 TT genotype) Prior history of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Use with caution in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs. TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).	Obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration >4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input). In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time.

Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	EFV, continued	*Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration **Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children.	However, evidence is conflicting about whether EFV use increases the incidence of suicidality.			
	RPV	Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/ nightmare *Other CNS Manifestations:* • Headache • Dizziness • Insomnia	In Adults: • CNS/neuropsychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients, and were severe requiring RPV discontinuation in 1% of patients. In Children: • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years to 17 years. Severe depressive disorders were reported in 5.6% of patients, including a suicide attempt in 1 subject.	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in case of severe symptoms.
	RAL	Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression	Children: • Increased psychomotor activity reported in one child. Adults: • Headache • Insomnia (<5% in adult trials)	Elevated RAL concentrations Co-treatment with TDF or PPI Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms.

Table 12a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System (CNS) Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	DTG	Onset: • 7–30 days after initiating drug Presentation *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation attempt, behavior, or completion *Other CNS Manifestations (Generally Mild):* • Insomnia • Dizziness • Headache	Adults • Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common, reported in up to 10% of patients. Less than 1% patients experienced more severe symptoms.	Pre-existing depression or other psychiatric illness	Use with caution in the presence of psychiatric illness especially depression	For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. Discontinuation resulted in resolution of neuropsychiatric symptom in 3 out of 4 patients (in the 4th patient, symptoms resolved slowly despite DTG continuation). For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.
Intracranial Hemorrhage	TPV	Onset: • 7–513 days after starting TPV	Children: • No cases of ICH reported in children. Adults: • In premarket approval data in adults, 0.23/100 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases.	Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported.	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.
Cerebellar Ataxia	RAL	Onset: • As early as 3 days after starting RAL Presentation: • Tremor • Dysmetria • Ataxia	Two cases reported in adults during post-marketing period.	Unknown; a speculated mechanism may include recent treatment with ATV with residual UGT1A1 enzyme inhibition and increased RAL serum concentration.	Use with caution with ATV or other drugs that cause strong inhibition of UGT1A1 enzyme.	Consider drug discontinuation. RAL reintroduction can be considered if predisposing factor (e.g., drug-drug interaction) identified and removed.

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; PPI = proton pump inhibitor; py = patient years; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

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Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Dyslipidemia	PIs: • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. NRTIs: • Especially d4T NNRTIs: • EFV > NVP, RPV, and ETR	Onset: • As early as 2 weeks to months after beginning therapy Presentation *PIs:* • ↑LDL-C, TC, and TG *NNRTIs:* • ↑LDL-C, TC, and HDL-C *NRTIs:* • ↑LDL-C, TC, and TG	Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/RTV 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. In studies of treatment naive adults, 38% and 32% receiving EVG/COBI/FTC/TAF developed abnormal fasting TC and LDL-C (respectively) after 48 weeks compared with 21% and 20% receiving EVG/COBI/FTC/TDF, difference mainly attributable to TAF In 48 adolescents treated with EVG/COBI/FTC/TAF median change from baseline to	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution	Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling Monitoring[a] *Adolescents and Adults:* • Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (>2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy. *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain non-fasting screening lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. *Children with Lipid Abnormalities and/or Additional Risk Factors:* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3	Assessment of additional CVD risk factors should be done in all patients. HIV-infected patients are considered to be at moderate risk of CVD.[b] Counsel on lifestyle modification, dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars particularly in case of ↑TG, elimination of trans fat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. If receiving d4T, it should be discontinued. If receiving PI-based ART, consider switching to a new PI-sparing ART regimen or PI-based regimen containing boosted ATV or DRV, which are less likely to cause lipid abnormalities. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treatment in children receiving ARV drugs at cut points recommended by NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.[b] The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL.

Table 12b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			weeks 24 and 36 were 26 mg/dl and 36 mg/dl, respectively for fasting TC, and 10 mg/dl and 17 mg/dl, respectively for direct LDL-C.		months after starting lipid therapy. • If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.	Initiate Drug Therapy Promptly in Patients with Fasting TG ≥500 mg/dL: Statins such as pravastatin, atorvastatin, or rosuvastatin.[c] Ezetimibe can be considered in addition to statins.[d] Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.[c] Risks must be weighed against potential benefits. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used as alternative agents for adults with ↑TG but are not approved for use in children. The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from non-fasting blood samples and follow up abnormal values with a test done in the fasted state.

[b] Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

[c] The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

[d] Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged ≥10 years. For additional information, see the PI, NNRTI, NRTI, and INSTI Drug Interactions Tables in the Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Key to Acronyms: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FLP = fasting lipid

profile; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TC = total cholesterol; TG = triglyceride lopinavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TC = total cholesterol; TG = triglyceride

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Table 12c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ Vomiting	Principally ZDV and PIs (e.g., LPV/r, RTV), but can occur with all ARVs and COBI	Onset: • Early Presentation: • Nausea, emesis—may be associated with anorexia and/or abdominal pain.	Varies with ARV agent; 10% to 30% in some series	Unknown	Instruct patient to take PIs with food. Generally improves with time; monitor for weight loss, ARV adherence.	Reassure patient/caretaker that nausea and vomiting will likely decrease over time. Provide supportive care, including instruction on dietary modification. Although antiemetics are not generally indicated, they may be useful in extreme or persistent cases.
Diarrhea	PIs (particularly NFV, LPV/r, FPV/r), buffered ddI, INSTI (mild)	Onset: • Early Presentation: • Generally soft, more frequent stools	Varies with ARV agent; 10% to 30% in some series	Unknown	Generally improves with time (usually over 6–8 weeks); monitor for weight loss, dehydration.	Exclude infectious causes of diarrhea. Although data in children on treatment of ARV-associated diarrhea are lacking, dietary modification, use of calcium carbonate (should not be used with DTG), bulk-forming agents (psyllium), or antimotility agents (loperamide) may be helpful. While there are few published data on its use, crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults but **not** in children.
Pancreatitis	ddI, d4T (especially concurrently or with TDF), boosted PIs Reported, albeit rarely, with most ARVs.	Onset: • Any time, usually after months of therapy Presentation: • Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis).	<2% in recent series Frequency was higher in the past with higher dosing of ddI.	Concomitant treatment with other medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced disease Previous episode of pancreatitis	Avoid use of ddI in patients with a history of pancreatitis.	Discontinue offending agent—avoid reintroduction. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

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Table 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	Principally ZDV	Onset: • Variable, weeks to months Presentation *Most Commonly:* • Asymptomatic or mild fatigue • Pallor • Tachypnea *Rarely:* • Congestive heart failure	HIV-Exposed Newborns: • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. HIV-Infected Children on ARVs: • 2–3 times more common with ZDV-containing regimens; less frequent with currently recommended dosing of ZDV	HIV-Exposed Newborns: • Premature birth • *In utero* exposure to ARVs • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • Malnutrition	HIV-Exposed Newborns: • Obtain CBC at birth. • Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or known to have low birth Hgb). HIV-Infected Children on ARVs: • Avoid ZDV in children with moderate to severe anemia when alternative agents are available. • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • Rarely require intervention unless Hgb is <7.0 g/dL or anemia is associated with symptoms. • Consider discontinuing ZDV if 4 weeks or more of a 6-week ZDV prophylaxis regimen are already completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, malignancies. • For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen; consider a trial of erythropoietin if essential to continue ZDV.
Macrocytosis	Principally ZDV; also d4T	Onset: • Within days to weeks of starting therapy • MCV often >100 fL Presentation: • Most often asymptomatic • Sometimes associated with anemia (occurs more often with ZDV than with d4T)	>90% to 95%, all ages	None	Obtain CBC as part of routine care.	None required unless associated with anemia

Table 12d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia[a]	Principally ZDV	Onset: • Variable Presentation: • Most commonly asymptomatic. Complications appear to be less than with neutropenias associated with cancer chemotherapy.	HIV-Exposed Newborns: • Rare HIV-Infected Children on ARVs: • 2.2% to 26.8% of children on ARVs, depending upon the ARV regimen. 2.2% for ZDV/3TC • Highest rates with ZDV-containing regimens	HIV-Exposed Newborns: • *In utero* exposure to ARVs • Combination ARV prophylaxis, particularly with ZDV plus 3TC HIV-Infected Children on ARVs: • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	HIV-Infected Children on ARVs: • Obtain CBC as part of routine care.	HIV-Exposed Newborns: • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/mm^3, or discontinue ARV prophylaxis entirely if ≥4 weeks of 6-week ZDV prophylaxis have been completed (see the Perinatal Guidelines[b]). HIV-Infected Children on ARVs: • Discontinue non-ARV marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen. Consider a trial of G-CSF if essential to continue ZDV.

[a] HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

[b] *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; d4t = stavudine; dL = deciliter; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) **(page 1 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatic Toxicity Elevated AST, ALT, clinical hepatitis	All ARVs may be associated with hepatitis. NVP and TPV are of particular concern. NVP, EFV, ABC, RAL, and MVC have been associated with hypersensitivity reactions. NRTIs (especially ZDV, ddI, and d4T) are associated with lactic acidosis and hepatic steatosis.	Onset: • Hepatitis generally occurs within the first few months of therapy, but can occur later. • Steatosis presents after months to years of therapy. • HBV-coinfected patients may develop severe hepatic flare with the initiation, withdrawal, or development of resistance to 3TC, FTC, or TDF (especially in patients receiving only one anti-HBV agent). • Hepatitis may also represent IRIS early in therapy, especially in HBV- and HCV-infected patients. Presentation: • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may be component of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis.	Uncommon in children Frequency varies with different agents and drug combinations.	HBV or HCV coinfection Elevated baseline ALT and AST Other hepatotoxic medications (including herbal preparations such as St. John's wort [*Hypericum perforatum*], Chaparral [*Larrea tridentate*], Germander [*Teucrium chamaedrys*]) Alcohol use Underlying liver disease Pregnancy For NVP-Associated Hepatic Events in Adults: • Female with pre-NVP CD4 count >250 cells/mm^3 • Male with pre-NVP CD4 count >400 cells/mm^3 Certain HLA types are also associated with NVP-associated hepatic events but are population-specific.[a] Higher drug concentrations for PIs, particularly TPV.	Prevention: • Avoid concomitant use of hepatotoxic medications. • If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP. Monitoring: *For ARVs Other Than NVP:* • Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., HBV- or HCV-coinfected or elevated baseline AST and ALT). *For NVP:* • Obtain AST and ALT at baseline, at 2 and 4 weeks, then every 3 months.	Asymptomatic patients with elevated ALT or AST should be evaluated for other causes and monitored closely (including repeating AST, ALT and checking total bilirubin). If ALT or AST is more than 5–10 times ULN and felt to be possibly or probably associated with ARVs, the potentially offending ARVs should be discontinued. In symptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restarting the offending agent. If a symptomatic hepatic event occurs on NVP, permanently discontinue drug (see also NVP Hypersensitivity). When clinical hepatitis is associated with lactic acidosis, avoid restarting the most likely agent, including ZDV, d4T, and ddI in particular (see also Lactic Acidosis). Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 12e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Indirect Hyperbilirubinemia	IDV, ATV (with either RTV or COBI)	Onset: • First months of therapy Presentation: • Jaundice; otherwise asymptomatic elevation of indirect bilirubin levels with normal AST, and ALT. Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.	HIV-Infected Children Receiving ATV: • In long-term follow-up, 9% had at least 1 total bilirubin level > 5 x ULN and 1.4% experienced jaundice	N/A	Monitoring: • No specific monitoring.	Not necessary to discontinue the offending agent except for cosmetic reasons. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time.
Non-Cirrhotic Portal Hypertension	ddI, d4t	Onset: • Generally after years of therapy Presentation: • GI bleeding, esophageal varices, hypersplenism • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism) • Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis.	Rare: • Probably less than 1%	Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T	Monitoring: • No specific monitoring	Manage complications of GI bleeding and esophageal varices. Discontinue/replace d4T or ddI, if patient is receiving either.

[a] For example, HLA-DRB1*0101 in whites, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and whites.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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Table 12f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	Several NRTIs (e.g., d4T, ZDV, ddI) Several PIs (e.g., LPV/r; less often ATV, ATV/r, DRV/r, NFV, TPV/r)	Onset: • Weeks to months after beginning therapy; median of 60 days (adult data). Presentation *Most Commonly:* • Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay *Also Possible:* • Frank DM (i.e., polyuria, polydipsia, polyphagia, fatigue, hyperglycemia)	Insulin Resistance *ARV-Treated Adults and Children:* • 6% to 33% Impaired Fasting Glucose *ARV-Treated Adults:* • 3% to 25% *ARV-Treated Children:* • 0% to 7% Impaired Glucose Tolerance *ARV-Treated Adults:* • 16% to 35% *ARV-Treated Children:* • 3% to 4% DM *ARV-Treated Adults:* • 0.6–4.7 per 100 person-years (2- to 4-fold greater than that for HIV-uninfected adults) *ARV-Treated Children:* • Rare in HIV-infected children	Risk Factors for Type 2 DM: • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	Prevention: • Lifestyle modification • Although uncertain, avoiding the use of d4T may reduce risk. Monitoring: • Monitor for polydipsia, polyuria, polyphagia, change in body habitus, and acanthosis nigricans. *Obtain RPG Levels at:* • Initiation of ARV therapy • 3–6 months after therapy initiation • Once a year thereafter *For RPG ≥140 mg/dL:* • Obtain FPG performed after 8-hour fast and consider referral to endocrinologist.	Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increased physical activity; cessation of smoking); consider consultation with dietician. Change NRTI (e.g., from d4T, ZDV, or ddI to TDF or ABC). For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL: • Patient meets diagnostic criteria for DM; consult endocrinologist. FPG 100–125 mg/dL: • Impaired FPG is suggestive of insulin resistance; consult endocrinologist FPG <100 mg/dL: *Normal FPG, but Does Not Exclude Insulin Resistance:* • Recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. *Insulin resistance* is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a 75g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75g); and *diabetes mellitus* as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, HgbA1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; DRV/r = ritonavir-boosted darunavir; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = ritonavir-boosted lopinavir; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TDF = tenofovir disoproxil fumarate; TPV/r = ritonavir-boosted tipranavir; ZDV = zidovudine

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Table 12g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic Acidosis	NRTIs, in particular, d4T and ddI (highest risk when co-administered)	Onset: • 1–20 months after starting therapy (median onset 4 months in 1 case series) Presentation *Usually Insidious Onset of a Combination of Signs and Symptoms:* • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea or vomiting • Dyspnea • Peripheral neuropathy **Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure).	Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L) *Adults:* • 15% to 35% of adults receiving NRTI therapy for longer than 6 months *Children:* • 29% to 32% Symptomatic Severe Hyperlactatemia (>5.0 mmol/L) *Adults:* • 0.2% to 5.7% Symptomatic Lactic Acidosis/Hepatic Steatosis: • Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%)	Adults: • Female gender • High BMI • Chronic HCV infection • African-American race • Prolonged NRTI use (particularly d4T and ddI) • Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline) • Co-administration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy Preterm Infants: • Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution)	Prevention: • Avoid d4T and ddI individually; co-administration of d4T and ddI is not recommended in an ARV regimen (no exception). • Due to the presence of propylene glycol as a diluent, LPV/r oral solution should never be used in preterm neonates in the immediate postnatal period. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. Monitoring *Asymptomatic:* • Measurement of serum lactate is not recommended. *Clinical Signs or Symptoms Consistent with Lactic Acidosis:* • Obtain blood lactate level.[a] Additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (Confirmed with Second Test): • Consider replacing ddI and d4T with other ARVs. • As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup. Lactate >5.0 mmol/L (Confirmed with Second Test)[b] or >10.0 mmol/L (Any 1 Test): • Discontinue all ARVs. • Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). Anecdotal (Unproven) Supportive Therapies: • Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC), and monthly monitoring of lactate for at least 3 months.

[a] Blood for lactate determination should be collected, without prolonged tourniquet application or fist clenching, into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

[b] Management can be initiated before the results of the confirmatory test.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane

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Table 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	Onset: • Trunk and limb fat initially increase within a few months of start of ART; peripheral fat wasting may not appear for 12 to 24 months after ART initiation.	Varies greatly depending upon measure and comparator group Highly Variable in Adults: • Up to 93% Children: • Up to 34%, perhaps more common in adolescents than prepubertal children	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	See below.	See below Although more typically associated with certain ARVs (e.g., d4T), a regimen review with consideration of changing the regimen should be considered, whenever present
Central Lipohypertrophy or **Lipo-accumulation**	Can occur in the absence of ART, but most associated with PIs and EFV.	Presentation: • Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females, particularly with EFV. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy).	Adults: • Up to 93% Children: • Up to 27%	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Calorically appropriate low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio	Calorically appropriate healthy diet low in saturated fats and simple carbohydrates, and exercise, especially strength training Smoking cessation (if applicable) to decrease future CVD risk Consider switching from PIs and EFV to an INSTI Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Recombinant human growth hormone • Growth hormone-releasing hormone • Metformin • Thiazolidinediones • Anabolic steroids • Liposuction.

Table 12h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Facial/Peripheral Lipoatrophy	Most associated with thymidine analogue NRTIs (d4T > ZDV)	Presentation: • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Adults: Up to 59% (particularly in patients on d4T-containing regimens) Children: • Up to 47% (particularly in patients on d4T-containing regimens) • Risk lower (up to 15%) in patients not treated with d4T or ZDV.	Underweight before ART	Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.	Replace d4T (not widely used and recommended only in special circumstances) or ZDV with other NRTIs if possible without loss of virologic control. Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • Thiazolidinediones.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CVD = cardiovascular disease; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

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See the archived version of Supplement III, February 23, 2009 *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*, (http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.

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Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV, IDV Although DRV causes crystalluria, it is not associated with increased nephrolithiasis risk.	Onset: • Weeks to months after starting therapy Clinical Findings: • Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine	ATV-related nephrolithiasis occurs in <10%.	In adults, elevated urine pH (>5.7) Unknown in children	Prevention: • Maintain adequate hydration. Monitoring: • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control; consider using alternative ARV.
Renal Dysfunction	TDF	Onset: • Variable; in adults, weeks to months after initiation of therapy. • Hypophosphatemia appears at a median of 18 months. • Glucosuria may have onset after a year of therapy. Presentation: *More Common:* • Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness. *Less Common:* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	Adults: • Approximately 2% with increased serum creatinine • Approximately 0.5% with severe renal complications Children: • Approximately 4% with hypophosphatemia or proximal tubulopathy; higher with prolonged TDF therapy, in advanced HIV infection or concomitant use of ddI	Risk May Be Increased in Children: • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Concurrent use of ddI or PIs (especially LPV/r), and preexisting renal dysfunction • Risk increases with longer duration of TDF treatment.	Monitor urine protein and glucose or urinalysis, and serum creatinine at 3- to 6-month intervals. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also measure serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time. While unproven, routine monitoring intervals of every 3–6 months might be considered. Abnormal values should be confirmed by repeat testing, and frequency of monitoring can be increased if abnormalities are found and TDF is continued.	If TDF is the likely cause, consider using alternative ARV.

Table 12i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated March 1, 2016; last reviewed March 1, 2016) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Elevation in Serum Creatinine	DTG, COBI, RPV	Onset: • Within a month of starting treatment Presentation: • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in GFR.	Common Need to distinguish between true change in GFR and other causes. True change might be associated with other medical conditions, continuing rise of serum creatinine with time, and albuminuria.	N/A	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or increases are ongoing with time.	No need to change therapy. Reassure patient about the benign nature of the laboratory abnormality.

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; GFR = glomerular filtration rate; IDV = indinavir; LPV/r = boosted lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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Table 12j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	Any ART regimen Specific Agents of Possible Concern: • TDF • PIs, especially LPV/r	Onset: • Any age; more common in months after initiation of ART. Presentation: • Most commonly asymptomatic; fracture (rare) • Osteoporosis diagnosis in children requires clinical evidence of bone fragility (e.g., fracture with minimal trauma) and cannot rely solely on measured low BMD.	Low BMD: • 7% of a U.S. cohort had a BMD z score less than or equal to –2.0 (87% treated with ART). • 24% to 32% of Thai and Brazilian adolescents had a BMD z score less than or equal to –2.0 (92% to 100% treated with ART).	Longer duration of HIV infection Greater severity of HIV disease Growth delay, pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprog-esterone use Limited weight-bearing exercise	Prevention: • Ensure sufficient calcium and vitamin D intake. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, steroid use). Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Consider obtaining serum 25-OH-vitamin D level.[a] • Obtain DXA.[b]	Ensure sufficient calcium intake and vitamin D sufficiency. Encourage weight-bearing exercise. Reduce modifiable risk factors (e.g., smoking, low BMI, use of steroids, use of medroxyprogesterone). Role of bisphosphonates not established in children Consider change in ARV regimen.

[a] Some experts would periodically measure 25-OH-vitamin D, especially in HIV-infected urban youth, because in that population, the prevalence of vitamin D insufficiency is high.

[b] Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with TDF. DXA could also be considered in adolescent women on TDF and medroxyprogesterone and in children with indications not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; DXA = dual-energy x-ray absorptiometry; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

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Osteopenia and Osteoporosis

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Table 12k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated March 1, 2016; last reviewed March 1, 2016)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency[a]	Risk Factors	Prevention/ Monitoring	Management
ARV Toxic Neuropathy[b]	d4T, ddI PIs	Onset: • Variable; weeks to months following NRTI initiation. Presentation: • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia (lowered pain threshold) • Allodynia (non noxious stimuli cause pain) • Decreased or absent ankle reflexes Distribution: • Bilateral soles of feet, ascending to legs and fingertips	HIV-Infected Children: • 1.13% prevalence (baseline 2001); incidence 0.23 per 100 person-years (2001–2006) in a U.S. cohort. • <1% discontinued d4T because of neuropathy in 3 large African cohorts (aged 1 month–18 years; median follow-up 1.8–3.2 years). • 42 out of 174 (24%) in a South African cohort were diagnosed with peripheral neuropathy. 86% were taking d4T, and use of ddI was an additional risk factor. • 4/40 (10%) Indian children taking d4T had abnormal nerve conduction tests. HIV-Infected Adults on d4T: • Prevalence up to 57% • Incidence rates of 6.4–12.1 per 100 person-years	HIV-Infected Adults: • Preexisting neuropathy (e.g., diabetes, alcohol abuse, vitamin B-12 deficiency) • Elevated triglyceride levels • Older age • Poor nutrition • More advanced HIV disease • Concomitant use of other neurotoxic agents (e.g., INH) • Some mitochondrial DNA haplogroups may have increased risk.	Limit use of d4T and ddI. As part of routine care, monitor for symptoms and signs of peripheral neuropathy.	Discontinue offending agent. Persistent pain can be difficult to treat; topical capsaicin 8% may be helpful. Consider referral to a neurologist. Data Are Insufficient to Allow the Panel to Recommend Use of Any of the Following Modalities in Children: • Tricyclic antidepressants • Gabapentin • Pregabalin • Mexiletine • Lamotrigine • Acupuncture or other complementary approaches

[a] Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

[b] HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

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Table 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 5, 2015; last reviewed March 5, 2015) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Rash	Any ARV can cause rash.	Onset: • First few days to weeks after starting therapy Presentation: • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. **Note:** Some rashes are the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major).	Common (>10% Adults and/or Children): • NVP, EFV, ETR, FPV, FTC Less Common (5% to 10%): • ABC, DRV, TPV, TDF Unusual (2% to 4%): • LPV/r, RAL, MVC, RPV	• Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV). • Possible association of polymorphisms in CYP2B6 and multiple HLA loci with rash with NVP.	When Starting NVP or Restarting After Interruptions >14 Days: • Once-daily dosing (50% of total daily dose) for 2 weeks, then escalation to target dose with twice-daily dosing is associated with fewer rashes.[a] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction. • Consider concomitant medications and illnesses that cause rash.	Mild-To-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement: • Most will resolve without intervention; ARVs can be continued while monitoring.[a] • Antihistamines may provide some relief. Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgias, Edema) and/or Rash Accompanied By Mucous Membrane Involvement (e.g., Conjunctivitis): • Manage as SJS/TEN/EM major (see below). Rash in Patients Receiving NVP: • Given elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP).
	ENF	Onset: • First few days to weeks after starting therapy Presentation: • Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time.	Adults and Children: • >90%	Unknown	• Routinely assess patient for local reactions. • Rotate injection sites. • Massage area after injection.	• Continue the agent as tolerated by the patient. • Adjust injection technique. • Rotate injection sites.

Table 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 5, 2015; last reviewed March 5, 2015) (page 2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
SJS/TEN/ EM Major	Many ARVs, especially NNRTIs (see frequency column)	Onset: • First few days to weeks after initiating therapy Presentation: • Initial rash may be mild, but often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia.	Infrequent: • NVP (0.3%), EFV (0.1%), ETR (<0.1%) Case Reports: • FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL	Adults: • Female gender • Race/ethnicity (black, Asian, Hispanic)	To Lower the Risk of Reactions to NVP when Starting or Restarting after Interruptions >14 Days: • Utilize once-daily dosing (50% of total daily dose) for 2 weeks, then escalate to target dose with twice-daily dosing, which is associated with fewer rashes.[a] • Counsel families to report symptoms as soon as they appear.	• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. • Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection. • Corticosteroids and/or IVIG are sometimes used, but use of each is controversial. • Do not reintroduce the offending medication. • In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs.
Systemic HSR With or without skin involve-ment and excluding SJS/TEN	ABC	Onset *With First Use:* • Within first 6 weeks *With Re-Introduction:* • Within hours Presentation: • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation. With re-challenge, symptoms can mimic anaphylaxis.	2.3% to 9% (varies by racial/ethnic group).	• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); also HLA-DR7, HLA-DQ3. • HSR risk is higher in those of white race compared to those of black or East Asian race.	• Screening for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is positive**. The medical record should clearly indicate that ABC is contraindicated. • When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness). • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not re-challenge with ABC even if the patient is HLA-B*5701-negative.

Table 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 5, 2015; last reviewed March 5, 2015) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involvement and excluding SJS/TEN	NVP	Onset: • Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy. • DRESS syndrome has also been described.	4% (2.5% to 11%)	Adults: • Treatment-naive with higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men). • Female gender (risk is 3-fold higher in females compared with males). Children: • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%.	When Starting NVP or Restarting After Interruptions >14 Days: • Two-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.[a] • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT in patients with rash. Obtain AST and ALT at baseline, before dose escalation, 2 weeks post-dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3 unless benefits outweigh risks. • Do not use NVP in PEP.	• Discontinue ARVs. • Consider other causes for hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated and monitor patient closely. • Do not re-introduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
	ENF, ETR	Onset: • Any time during therapy. Presentation: • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARVs. Re-challenge with ENF or ETR is not recommended.

Table 12l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated March 5, 2015; last reviewed March 5, 2015) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Systemic HSR With or without skin involvement and excluding SJS/TEN	RAL	DRESS syndrome	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARVs. Re-challenge with RAL is not recommended.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.	Discontinue all ARVs. Re-challenge with MVC is not recommended.

[a] The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. **NVP should be stopped and not restarted** if the rash is severe or is worsening or progressing.

Key to Acronyms: ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HSR = hypersensitivity reaction; IDV = indinavir; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = post-exposure prophylaxis; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

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